Traumatic Coagulopathy: Where are the Good Experimental Models?

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Background: The development of coagulopathy associated with trauma is a complex process that involves a combination of many factors. It is important to be able to model experimental trauma-related coagulopathy to explore preventative and therapeutic strategies, and numerous models of traumatic coagulopathy have been explored. This systematic review assessed the primary question "What are relevant experimental models with which to study early traumatic coagulopathy?" and secondary questions on mechanisms.

Methods: The author group reviewed 695 abstracts that resulted in 36 articles being fully reviewed by the group. The group identified 12 key studies (grade A) addressing the primary question. A further 10 articles were thought to be relevant but less important (grade B). Eight articles were considered worthwhile publications but not as relevant to the query (grade C), and six articles were considered not relevant after detailed review (grade D).

Results: This structured literature review demonstrated a lack of relevant models for human traumatic coagulopathy. We identify challenges in modeling traumatic coagulopathy and limitations to current experimental models and include a proposal for features of an "ideal" model of traumatic coagulopathy, but recognize that this involves major challenges.

Conclusions: Models of traumatic coagulopathy need to more closely resemble human physiology and real-life conditions if they are to influence clinical practice.

Key Words: Coagulopathy, Trauma, Experimental models, Review.

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Hemorrhagic shock is the second most common cause of death among trauma patients arriving at hospital, and is the most frequent cause of death in the early phase of hospital treatment.[1] The majority of trauma patients do not develop a life-threatening coagulopathy, but for those that do, the consequences are dramatic. It is, therefore, important to be able to model experimental trauma-related coagulopathy to explore preventative and therapeutic strategies.

The development of coagulopathy associated with traumatic injury is complex (Fig. 1), and involves a combination of many factors[2] including:

- Tissue injury and hemorrhage,
- Shock,
- Dilution,
- Activation and consumption of coagulation factors and platelets,
- Acidosis,
- Hypothermia,
- Activation of anticoagulant and fibrinolytic pathways,
- Inflammatory response,
- Hypocalcemia,
- Anticoagulant drugs for comorbid conditions, and
- In-born genetic variation or defects.

Among these, the six key initiators of coagulopathy in trauma patients appear to be: tissue trauma, shock, dilution, hypothermia, acidemia, and inflammation.[2]

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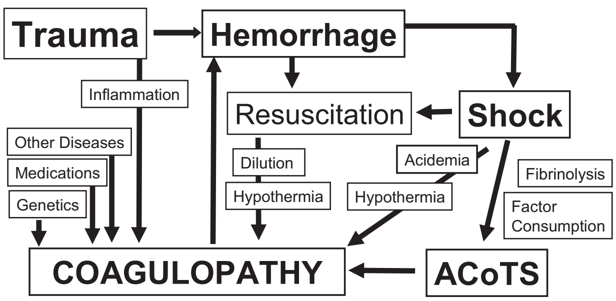

Fig. 1. *A graphic representation of factors currently thought to play a role in the development of coagulopathy after traumatic injury. ACoTS, acute coagulopathy of trauma-shock.*

Current models employed to study coagulopathy may be limited in their ability to reproduce these conditions, a difficulty that is reflected in the diversity of models that have been studied. The author group generated a series of structured queries related to current experimental models to study post-traumatic coagulopathy. The primary objective of the review was to identify relevant experimental models used to study early traumatic coagulopathy. Related objectives were to assess if experimental models have addressed the issues of (1) the mechanism of early traumatic coagulopathy, (2) differences between traumatic and other (dilutional) types of coagulopathy, (3) the role of hypothermia (4), the role of acidosis (5), the role of tissue injury, and (6) the role of factor depletion. These questions were used as the basis for a structured literature assessment, the findings of which are presented here.

MATERIALS AND METHODS

The primary query for the structured literature survey was defined as "What are relevant experimental models with which to study early traumatic coagulopathy?" Related queries investigated whether experimental models have addressed the issues of (1) the mechanism of early traumatic coagulopathy, (2) differences between traumatic and other (dilutional) types of coagulopathy, (3) the role of hypothermia, (4) the role of acidosis, (5) the role of tissue injury, and (6) the role of factor depletion.

Comprehensive literature searches were performed in December 2006 using the indexed online database MEDLINE/PubMed. Boolean operators and MeSH-thesaurus keywords were applied as a standardized use of language to unify differences in terminology into single concepts. The initial search strategy used the terms ("Models, Theoretical" [MeSH] OR "Experimental model") AND "Blood Coagulation Disorders" (MeSH) and "Wounds and injuries" (MeSH) with no limits on language or time period. A less restrictive search was then applied using the terms ("Models, Theoretical" [MeSH] OR "Experimental model") AND "Blood Coagulation Disorders" (MeSH) with no language limit but a time limit of 10 years. All the resulting abstracts identified by this search strategy were screened independently by two investigators (BB, DBH) to assess their relevance in relation to the objectives of the review and decisions on relevance were resolved by consensus. The full publications from relevant abstracts were then retrieved and distributed to the entire group. Experts in the field were consulted and lists of cited literature within relevant articles were also screened for relevant publications which were then retrieved for review. An updated abstract screen restricted to the current year was performed in October 2007.

Full publications were each reviewed by at least one investigator, and results presented to the entire group for discussion and consensus. The meetings aimed to identify literature relevant to the query and to assign a relevance score to each publication. The grading scale employed identified publications as (A) a key publication to support the query addressed, (B) a relevant publication, but of less importance, (C) a worthwhile publication, but less relevant to the query, or (D) a publication that after review was considered not relevant to this query. Burn models were retrospectively excluded from consideration because a different mechanism of coagulopathy is in effect during the first 3 days after injury. Publications describing experiments in human subjects were also excluded from this review. An internal validity assessment of the risk of selection, performance, attrition, and adjudication biases were not performed.

The author group comprises the independent international medical Educational Initiative on Critical Bleeding in Trauma (EICBT), which aims to increase awareness among health care professionals that coagulopathy during the first hour after traumatic injury may play an important role in patient outcomes. Members of the initiative were offered compensation for their presence at face-to-face meetings, but not for the time invested in screening and reviewing published literature or for article development and review. All of the authors contributed to the concept and design, data acquisition, data analysis and interpretation, article drafts and revision, and final approval of the submitted article. The EICBT group operates as an independent faculty managed by Physicians World GmbH, Mannheim, Germany. The activities of the EICBT are supported by unrestricted educational grants from Novo Nordisk A/S, Bagsvaerd, Denmark.

RESULTS

An initial structured literature search using MeSH terms ("Models, Theoretical" [MeSH] OR "Experimental model") AND "Blood Coagulation Disorders" (MeSH) and "Wounds and injuries" (MeSH) with no limits on language or time period resulted in 25 abstracts. A subsequent search applied using the terms ("Models, Theoretical" [MeSH] OR "Experimental model") AND "Blood Coagulation Disorders" (MeSH) with no language limit but a time limit of 10 years resulted in 695 abstracts. All of the retrieved abstracts were screened and 30 full publications assessed according to the selection criteria. Additional publications listed among the citations within the screened articles and identified by experts in the field were also reviewed. The process resulted in 36

Table 1 Characteristics of the Studies Described in the Full Publications Reviewed in this Structured Literature Survey

Author Year (Reference)	Grade	Model	RCT
Asakura 2003 (3)	A	Rat	−(CT)
Butenas 2000 (4)	A	Mathematical	−
Ho 2005 (5)	A	Mathematical	−
Howes DW 2007 (6)	A	Pig	+
Jewelewicz 2003 (7)	A	Pig	+
Jeroukhimov I 2003 (8)	A	Pig	+
Martini 2005 (9)	A	Pig	+
Martini 2006 (10)	A	Pig	+
Martini 2006 (11)	A	Pig	−(RT)
Martini 2007 (12)	A	Pig	+
Martinowitz 2001 (13)	A	Pig	+
Schwaitzberg 2004 (14)	A	Pig, dog and rabbit	−
Clarke 2002 (15)	B	Rabbit	−
Fries 2006 (16)	B	Pig	+
Hirshberg 2003 (17)	B	Mathematical	−
Lynn 2002 (18)	B	Pig	+
Martini 2005 (19)	B	Pig	+
Pergolizzi 2006 (20)	B	Mouse	−(CT)
Schreiber 2002 (21)	B	Pig	+
Schreiber 2003 (22)	B	Pig	+
Tran 2000 (23)	B	Sheep	−
Turecek 1997 (24)	B	Rabbit	−CT
Anagnostopoulos 2001 (25)	C	Pig	−
Gilles 2000 (26)	C	Mouse	−
Klemcke 2005 (27)	C	Pig	±
Niedner 1980 (28)	C	Fetal rabbit	−
Niedner 1980 (29)	C	Fetal rabbit	−
Niedner 1980 (30)	C	Fetal rabbit	−
Stief 2006 (31)	C	Cellular in vitro	−
Taylor 2000 (32)	C	Baboon	−
Denis 1998 (33)	D	Mouse	−
Kruithof 1997 (34)	D	Baboon	−CT
Lei 2005 (35)	D	Mouse	−
Norman 2003 (36)	D	Mouse	−
Okajima 2000 (37)	D	Cellular in vivo	−
Sauger 2005 (38)	D	Pig	−

Grading scale: A, key publication to support the question addressed; B, relevant publication, but of less importance; C, worthwhile publication, but not relevant to question; D, publication not relevant to this query.

RCT, randomized controlled trial; CT, controlled trial; RT, randomized trial.

full publications that were reviewed by the author group and are listed in Table 1.

Study Characteristics

The studies assessed featured six different animal species, the most common being porcine models, which were used in 17 of the studies assessed, a mouse model used in 5, a rabbit model in 3, a rabbit fetus model in 3, a baboon model in 2, a rat model in 1 study, a dog model in 1, and a sheep model in 1 study. Human cellular in vivo and in vitro models were used in two, and mathematical modeling was used in three studies. There were 13 porcine randomized controlled trials, 4 controlled trials, and 1 randomized trial the remainder were case series or mathematical models. Animal models involved anesthesia and ventilatory support. Nine of the studies featured severe traumatic liver injury in a porcine model. Studies usually involved small sample sizes and were usually unblinded for interventions. Hypothermia was generated using several methods, including cooling blankets, leaving the abdomen open or intra-abdominal cold fluid lavage. Different methods were used to generate acidosis including umbilical cord clamp in the rabbit fetus model and infusion of hydrochloric acid in one porcine model. The sequence of interventions often involved red cell loss, fluid hemodilution, hypothermia or acidosis or both before the generation of a traumatic organ injury. Different resuscitation fluids were employed, including crystalloids (Ringers,[10,11,19,22,27] saline[15,19,23] and colloids 6% hetastarch,[7,13,16] 5% albumin[21]). The periods of observation for blood loss and survival effects were often short.

The group identified 12 key studies (grade A) that addressed relevant experimental models with which to study early traumatic coagulopathy. A further 10 articles were thought to be relevant but less important (B). Eight articles were considered worthwhile publications but not very relevant to the query (C). Articles evaluated and grades assigned are listed in Table 1.

Five of the nine grade A studies involved similar studies in a porcine model.[9–13] In the simplest experiments, anesthetized pigs were rendered acidotic by infusion of hydrochloric acid, hypothermic by use of a cooling blanket, internal cooling, or both, and a variety of coagulation parameters were measured. Both hypothermia and acidosis increased the bleeding time from a standardized splanchnic injury.[19] Hypothermia primarily delayed the onset of thrombin generation, whereas acidosis strongly affected thrombin generation rates. The combination of hypothermia and acidosis increased bleeding time more than either factor alone. Other studies examined the metabolism of fibrinogen. Hemorrhagic shock with or without fluid resuscitation was found to increase the breakdown of fibrinogen, without affecting its rate of synthesis.[9] Reversal of acidosis with either bicarbonate solution or tris-hydroxymethylaminomethane was found to increase serum pH but to have no effect on coagulation kinetics.[11] A similar model used pigs that were first cooled, then hemodiluted by exchange transfusion, and then subjected to a grade V liver injury.[13] Coagulopathy at this time point was indicated by increased prothrombin time and decreased levels of platelets and fibrinogen. Administration of recombinant factor VIIa was found to reduce blood loss and restore coagulation.

One study examined coagulation in rats treated with either tissue factor or lipopolysaccharide to induce coagulopathy.[3] Although either treatment resulted in decreased platelets and fibrinogen and increased thrombin–antithrombin complexes, there were important differences noted. Coagulopathy induced by lipopolysaccharide (the presumed mechanism for human disseminated intravascular coagulation resulting from sepsis) also severely depressed antithrombin III and led to significantly worse organ system failure and higher mortality. Coagulopathy induced by tissue factor (1 mechanism associated with major tissue trauma) led to increased D-dimer levels but less organ failure and lower mortality. This study presented an important lesson in the importance of the mechanism of coagulopathy, and the need to design experimental models carefully.

Two other grade A studies used mathematical modeling to examine the effects of dilution and resuscitation on coagulation function. In the first, the importance of various clotting factors on the rates of clot initiation and propagation were modeled across a range of dilutions.[4] Clot initiation is most sensitive to the concentration of FVIIa, whereas clot propagation rate is largely determined by the concentrations of prothrombin and antithrombin III. In the second publication, rapid bleeding and rapid fluid resuscitation were modeled using different ratios of administered plasma and red blood cell.[5] Coagulation factor concentration and hematocrit were best preserved when the ratio of plasma to red blood cell was approximately 1:1 before the onset of coagulopathy, and 1.5:1 when coagulopathy was already present. Although these mathematical models are useful for strategic thinking about the treatment of coagulopathy, they lack many of the tactical variables (hypothermia, acidosis, tissue injury, and inflammation) that complicate clinical care.

Of the 10 grade B studies, 5 also employed porcine models[16,18,19,21,22] to examine hepatic injury,[16,18,21,22] the role of temperature and acidosis,[19] and factor VIIa.[21,22] The remaining grade B studies included two rabbit model studies,[15,24] focused on the role of factor VII in an endotoxin model[15] and antibody-induced hemophilia in a von Willebrand factor model,[24] a mathematical model of dilutional coagulopathy,[17] gene therapy enhanced clotting in a murine von Willebrand model[20] and a sheep model of thoracic aortic surgery-induced coagulopathy.[23]

Most of the studies featured small sample sizes, unblinded interventions, and the periods of observation for blood loss and survival effects were significantly shorter than those that would be expected during routine human trauma management.

DISCUSSION

This structured literature review demonstrated an overall lack of relevant models for human traumatic coagulopathy. Although many studies of coagulation and coagulopathy were identified, there were none that accurately modeled all of the mechanisms present in human traumatic hemorrhage. Worse, some of the studies identified actually cast doubt on the results of others, e.g., the documented differences in mechanism between coagulopathy induced by tissue factor versus lipopolysaccharide.[3] The diversity of models and methods that have been developed to study coagulopathy without a satisfying standard likely reflects the fact that the physiology of human traumatic coagulopathy is not yet fully understood and is likely to be very difficult to model.

Porcine models of coagulopathy were judged useful because they use a large mammalian species, they incorporate both hypothermia and dilutional effects and they include uncontrolled hemorrhage. Significant differences relative to the human trauma patient do exist, however, and include the lack of diffuse tissue injury and the presence of a deep level of anesthesia. Anesthesia and sedation, which are ethical necessities in animal models, are known to influence the inflammatory response to injury and alter compensatory physiology. This nonpathophysiologic sequence of insults (compared with human trauma) has an unknown effect on the overall response in the models used. We know that human trauma patients presenting to emergency departments already have a common and clinically important acute traumatic coagulopathy that is not related to fluid administration, is a marker of injury severity, and is an independent predictor of mortality.[39–41] Modeling the true pathophysiologic sequence of human traumatic coagulopathy in a whole animal model would not meet the requirements of the ethical review process. Further differences include the means by which acidosis is induced, and the need to "knock down" the coagulation system, a process that is more efficient in some mammals than in humans,[42–44] to achieve "coagulopathy." This sequence dictates that injury occurs only after other insults have taken place. The overall effect of large tissue injury on coagulopathy in an animal model is lacking. The association of inflammation and trauma was considered in the four sepsis model studies included in this review as having relevance[3,15,31,32] and emphasizes the emerging understanding of similarities and differences between sepsis and tissue trauma as triggers for coagulopathy.[41]

Anatomic and size differences limit the implications of these studies for human management. Hypothermia is often generated by central cooling, which may be significantly different from the hypothermia observed in human trauma victims. The applicability of the different methods of generating acidosis (umbilical cord clamp in the rabbit fetus model and infusion of hydrochloric acid in porcine models) are debatable. The intolerance of pigs to the infusion of lactic acid (as a more relevant means of studying acidosis) demonstrates a major species difference that may impact the interpretation of other porcine models. When lactate alone was infused into pigs, hemolysis occurred in most animals, and the degree of acidosis produced was difficult to control. Some pigs died at one concentration whereas others did not.[19] This sequence of induced hypothermia and acidosis is also very different from the spontaneous hypothermia and acidosis seen after traumatic injury, where blood loss, causing shock and ischemia, is the factor that triggers lactic acidosis.

None of the models comprehensively account for or assess all of the variables that are involved in generating traumatic coagulopathy in humans. This is no doubt a reflection of the complexity of human trauma associated coagulation failure and a parallel deficiency in the models. Current experimental models have only limited ability to address the mechanisms of early traumatic coagulopathy while differentiating between traumatic and other types of coagulopathy (e.g., dilutional coagulopathy). The hypothermia and acidosis generated in the models studied may exert their effects using mechanisms that are significantly different from the human situation, which may in turn limit the implications for clinical practice. The role of tissue injury and specific factor depletion are not well assessed in current models.

There are obvious difficulties in proposing an "ideal model" for the study of traumatic coagulopathy, but the author group thinks that the following elements are important. The ideal model

- Should comprise a mammalian species, and a model that is similar to humans in size is probably better than a smaller species,
- Should critically consider the manner in which the mammal's clotting system is "knocked down" to simulate humans, whether by prebleeding, dilution, or genetics (genetic knockout),
- Should incorporate significant tissue injury,
- Should include blood loss and resuscitation before assessing dilution, hypothermia, and acidosis,
- Should incorporate a dilutional component, simulating clinical resuscitation practice,
- Should incorporate hypothermia,
- Should incorporate acidosis,
- Should measure inflammatory markers, especially protein C and
- Should assess anticoagulant and fibrinolytic pathways.

Although this sort of model clearly presents a major challenge to investigators, these factors will make the resulting studies more clinically relevant. The current deficiencies also underline the need for careful human study. Major progress in the future, particularly with pharmaceutical therapies, is likely to rely heavily on the study of relevant models.

Summary

The author group reviewed 695 abstracts that resulted in 36 articles being fully reviewed by the group. The group identified 12 key studies (grade A) addressing the primary question. A further 10 articles were thought to be relevant but less important (grade B). Eight articles were considered worthwhile publications but not as relevant to the query (grade C), and six articles were considered not relevant after detailed review (grade D).

This structured literature review demonstrated a lack of relevant models for human traumatic coagulopathy. We identified challenges in modeling traumatic coagulopathy and limitations to current experimental models. We include a proposal for features of an "ideal" model of traumatic coagulopathy, but recognize that this involves major challenges. Models of traumatic coagulopathy need to more closely resemble human physiology and real-life conditions if they are to be useful in clinical practice.

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